

Heritability of Strabismus: Genetic Influence Is Specific to Eso-Deviation and Independent of Refractive Error

Paul G. Sanfilippo,¹ Christopher J. Hammond,² Sandra E. Staffieri,¹ Lisa S. Kearns,¹ S. H. Melissa Liew,² Julie M. Barbour,³ Alex W. Hewitt,¹ Dongliang Ge,⁴ Harold Snieder,^{2,5} Jane R. MacKinnon,⁶ Shayne A. Brown,¹ Birgit Lorenz,⁷ Tim D. Spector,² Nicholas G. Martin,⁸ Jeremy B. Wilmer,⁹ and David A. Mackey^{1,10}

¹Centre for Eye Research Australia, Department of Ophthalmology, Royal Victorian Eye and Ear Hospital, University of Melbourne, Melbourne, Victoria, Australia

²Department of Twin Research and Genetic Epidemiology, School of Medicine, King's College London, London, UK

³The Launceston Eye Institute, Launceston, Tasmania, Australia

⁴Center for Human Genome Variation, Duke University School of Medicine, Durham, NC, USA

⁵Unit of Genetic Epidemiology and Bioinformatics, Department of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

⁶Department of Ophthalmology, Royal Hobart Hospital, University of Tasmania, Tasmania, Australia

⁷Department of Ophthalmology, Justus Liebig University, Giessen, Germany

⁸Genetic Epidemiology Unit, Queensland Institute for Medical Research, Brisbane, Queensland, Australia

⁹Department of Psychology, Wellesley College, Wellesley, MA, USA

¹⁰Lions Eye Institute, Centre for Ophthalmology and Visual Science, University of Western Australia, Perth, Australia

Strabismus represents a complex oculomotor disorder characterized by the deviation of one or both eyes and poor vision. A more sophisticated understanding of the genetic liability of strabismus is required to guide searches for associated molecular variants. In this classical twin study of 1,462 twin pairs, we examined the relative influence of genes and environment in comitant strabismus, and the degree to which these influences can be explained by factors in common with refractive error. Participants were examined for the presence of latent ('phoria') and manifest ('tropia') strabismus using cover–uncover and alternate cover tests. Two phenotypes were distinguished: eso-deviation (esophoria and esotropia) and exo-deviation (exophoria and exotropia). Structural equation modeling was subsequently employed to partition the observed phenotypic variation in the twin data into specific variance components. The prevalence of eso-deviation and exo-deviation was 8.6% and 20.7%, respectively. For eso-deviation, the polychoric correlation was significantly greater in monozygotic (MZ) ($r = 0.65$) compared to dizygotic (DZ) twin pairs ($r = 0.33$), suggesting a genetic role ($p = .003$). There was no significant difference in polychoric correlation between MZ ($r = 0.55$) and DZ twin pairs ($r = 0.53$) for exo-deviation ($p = .86$), implying that genetic factors do not play a significant role in the etiology of exo-deviation. The heritability of an eso-deviation was 0.64 (95% CI 0.50–0.75). The additive genetic correlation for eso-deviation and refractive error was 0.13 and the bivariate heritability (i.e., shared variance) was less than 1%, suggesting negligible shared genetic effect. This study documents a substantial heritability of 64% for eso-deviation, yet no corresponding heritability for exo-deviation, suggesting that the genetic contribution to strabismus may be specific to eso-deviation. Future studies are now needed to identify the genes associated with eso-deviation and unravel their mechanisms of action.

■ **Keywords:** twins, heritability, ophthalmology, strabismus

Comitant strabismus (heterotropia or squint) is a complex disorder characterized by constant or intermittent ocular misalignment that often results in reduced or absent binocular vision and subsequent amblyopia of the deviated eye.

RECEIVED 11 January 2012; ACCEPTED 25 January 2012. First published online 13 June 2012.

ADDRESS FOR CORRESPONDENCE: Professor David A Mackey, Lions Eye Institute, Centre for Ophthalmology and Visual Science, University of Western Australia, 2 Verdun St., Nedlands, WA 6009, Australia. E-mail: D.Mackey@utas.edu.au

The condition affects 2–6% of the general population and is the most common cause of poor vision in childhood (Graham, 1974; Robaei et al., 2006; Williams et al., 2008). Comitant strabismus is not associated with systemic abnormality and is marked by non-restrictive, non-paralytic ocular misalignment of the same magnitude in all directions of gaze. There are two primary forms of horizontal comitant strabismus (hereafter referred to as ‘strabismus’): esotropia (convergent strabismus in which one or both eyes turn inwards) and exotropia (divergent strabismus in which one or both eyes turn outwards). In contrast, the more common form of ocular motor status, heterophoria, represents a ‘latent’ type of strabismus in which binocular vision functions normally except under certain conditions such as tiredness or illness, or that which may give rise to asthenopic (eye-strain) symptoms. Like manifest strabismus, heterophoria can be classified by the direction of horizontal deviation (esophoria — inwards, exophoria — outwards). Binocular vision status, the type and magnitude of deviation and the differentiation of heterophoria and heterotropia may be assessed with the cover test. It is important to distinguish that although disease-causing genes and loci have been identified for incomitant strabismus, often referred to as congenital cranial dysinnervation disorders (Engle, 2007; Gutowski et al., 2003; Traboulsi, 2007), currently we have limited understanding of the more prevalent comitant type, the focus of the current study.

Notwithstanding the lack of definitive data in the literature on the etiological foundation for strabismus, it is often assumed to be a multifactorial anomaly with both genetic and environmental risk factors. The tendency for the disorder to run in families, which could result from either genetic or environmental factors, has been recognized for centuries, with Hippocrates reporting in 400 BC that ‘children of parents having distorted eyes squint for the most part’ (Jones, 1886). More recent studies have confirmed a higher prevalence of strabismus among families of an affected individual than among the general population (Abrahamsson et al., 1999; Cross, 1975; Podgor et al., 1996; Waardenburg, 1954; Ziakas et al., 2002). Twin studies, which allow genetic and environmental influence to be distinguished, have shown higher concordances for strabismus within identical (monozygotic [MZ]) twin pairs compared to their non-identical (dizygotic [DZ]) counterparts, thus supporting a genetic contribution to the disorder (Wilmer & Backus, 2009). Recently, Wilmer and Backus published a critical review and meta-analysis of twin strabismus literature. Based on 3,096 4- to 7-year-old twin pairs in studies that met acceptable methodological standards, the meta-analysis estimated a high 92% genetic contribution to strabismus (Wilmer & Backus, 2009). However, due to insufficient subtyping in prior studies, the authors were unable to examine convergent (eso) and divergent (exo) subtypes of strabismus separately nor did prior studies contain enough information to evaluate whether

strabismus and refractive error share a common genetic basis.

Environmental risk factors have also been observed to predict one’s susceptibility to strabismus. Neonatal risk factors such as low birth weight and prematurity may be associated with the disorder developing in childhood (Bremer et al., 1998; Chew et al., 1994; Keith & Kitchen, 1983; Robaei et al., 2006; Torp-Pedersen et al., 2010; Williams et al., 2008). This is supported by the fact that twins, commonly born premature and with low birth weight, have a higher prevalence of strabismus than the general population (Wilmer & Backus, 2009). Moreover, DZ twins, who share a common prenatal environment, demonstrate higher strabismus concordance than full siblings (even after accounting for different prevalences between twins and singletons) (Wilmer & Backus, 2009). Several studies have found that maternal smoking during pregnancy predicts disrupted visual development (Chew et al., 1994; Christianson, 1980; Hakim & Tielsch, 1992). Our previous work from the Twins Eye Study in Tasmania (TEST) similarly found that maternal smoking predicts delayed age at first crawling or walking, potentially due to adverse impacts on vision (Ponsonby et al., 2007). Additionally, in the Danish National Birth Cohort (DNBC) of 96,842 children, large head circumference and congenital abnormalities — possibly affected by environmental factors — were associated with increased risk of strabismus (Torp-Pedersen et al., 2010).

We evaluated the heritability of strabismus in a large twin population. To our knowledge, this is the first large study to utilize clinical data (rather than parental reporting) or to distinguish between eso- and exo-deviations. Furthermore, this work is novel in examining the genetic association between refractive error and strabismus and the magnitude of potential pleiotropic effects.

Methods

Participants

Twin pairs were identified from three cohorts: the TEST (Mackey et al., 2009), the Australian Twins Eye Study (ATES) (Wright & Martin, 2004), and the TwinsUK Adult Twin Registry based at St Thomas’ Hospital in London (Spector & Williams, 2006). The vast majority of subjects were Caucasian. The TEST and ATES cohorts consisted of younger twin pairs of both sexes in contrast to the predominantly older, female demographic of the UK Twins group (the Registry was originally established to study osteoporosis). Recruitment was conducted without providing subjects with knowledge of specific hypotheses or eye studies being conducted, reducing ascertainment bias. The relevant ethics committees of the Royal Victorian Eye and Ear Hospital, University of Tasmania, and St Thomas’ Hospital approved the study. The study adhered to the tenets of the Declaration of Helsinki.

Examination Protocol

Subjects underwent a comprehensive clinical examination that included: assessment of binocular alignment, anterior segment examination, corneal pachymetry, intraocular pressure measurement, autorefraction, and a mydriatic optic disc assessment. A detailed ocular history was obtained including history of amblyopia, family history of strabismus, previous ocular surgery, and age at first wearing glasses. A cover–uncover and alternating cover test was performed on all subjects at standard near (33 cm) and far (6 m) test distances (Mackey et al., 2009). The presence of any ocular misalignment (manifest or latent) was recorded or, alternatively, in the absence of deviation, orthophoria was noted. Subjects with strabismus on examination associated with previous history of trauma or ocular surgery to correct the misalignment were excluded from the study. Stereoscopic depth perception was measured using the TNO test. Spherical equivalent and total astigmatism was recorded, in dioptres (D), for each eye. For all twin pairs, zygosity was confirmed by DNA analysis of short tandem-repeat and subsequent Genome-Wide Association Studies.

Statistical Analysis

Familial aggregation of a specific trait or disease occurs when relatives who share genes and/or environmental factors are more phenotypically similar than unrelated individuals. The twin study provides an ideal means for partitioning such familial aggregation into the effect of genes and shared environment on a phenotype of interest. The simplest method is to determine whether identical (MZ) twins raised together are more similar to each other for a given trait than non-identical (DZ) twins raised together. If a genetic basis for the trait exists, one would expect MZ twins to exhibit greater trait concordance or correlation as they share 100% of their genetic material, compared to DZ twins who on average share only 50%.

Data management and statistical tests were performed in the R statistical environment (R Development Core Team, 2010). Two phenotypes were examined: eso-deviation (esophoria and esotropia) and exo-deviation (exophoria and exotropia). A continuous ‘liability’ model was employed utilizing multiple thresholds to account for the categorical nature of the data. In this way an underlying normally distributed risk to strabismus in the population is assumed, which is affected by multiple genetic and environmental factors (Falconer & Mackay, 1996). Thus, each phenotype was classified in an ordinal manner: normal score = 0, phoria score = 1, and tropia score = 2. Structural equation modeling (SEM) was subsequently employed to fit the data to a saturated model in which polychoric correlations and thresholds were freely estimated. Genetic and environmental parameters that best fit the observed twin covariances were estimated directly from the raw categorical data using OpenMx software (Boker et al., 2011). Potential sex differences in the genetic and environmental influences

on strabismus were investigated by equating twin pair correlations in a stepwise manner for five zygosity groups: MZ males, MZ females, DZ males, DZ females, and DZ opposite-sex twins. ‘Quantitative’ sex differences were initially examined by equating correlations between MZ males and MZ females, and DZ males and DZ females (Neale & Cardon, 1992). ‘Qualitative’ sex differences were examined by equating correlations between same- and opposite-sex DZ pairs.

To determine heritability, a series of hierarchical models were fitted to the raw data and the significance of each assessed. Each of the nested sub-models was then compared to the full model by χ^2 tests. Twice the difference between log-likelihood values of the nested and full models is asymptotically distributed as χ^2 with degrees of freedom (*df*) equal to the difference in parameters being estimated. The Akaike information criterion (AIC) was used to determine the best-fitting mode by evaluating model parsimony (i.e., the best goodness-of-fit combined with the fewest latent variables). The model with the lowest AIC suggests the best fit. Results were adjusted for the covariate effects of age, sex, and refractive error (modeled as fixed effects). The observed phenotypic variation in the twin data may be partitioned into specific variance components: additive (A) genetic, dominant (D) genetic, and common (C) and unique (E) environmental variance components (the latter also including measurement error). Heritability is defined as the proportion of total phenotypic variation due to genetic effects $(A + D)/(A + D + C + E)$ (Sanfilippo et al., 2010).

For comparison between strabismus and refractive error, polychoric correlations were estimated using a saturated model, with refractive error divided into deciles to recode it from a continuous measurement to a categorical one, allowing it to be modeled with the categorical strabismus data. The univariate models were extended to include the bivariate case of spherical equivalent and strabismus, to allow assessment of the extent to which any correlation between these two variables could be explained by common genes.

Results

Data were available for 1,462 twin pairs (2,924 individuals) in total: 956 pairs (389 MZ, 567 DZ) from the Australian cohort (mean age 20.8 (± 12.7), range 5–90 years) and 506 pairs (226 MZ, 280 DZ) from the UK group (mean age 62.2 (± 5.7), range 49–79 years). In the saturated model, liability thresholds could be equated across birth order and zygosity without any loss in fit, indicating that the prevalence of strabismus is not contingent on birth order or zygosity. No quantitative or qualitative sex differences were observed as polychoric correlations could also be equated across zygosity groups stratified by sex without significant loss of model fit. Therefore, subsequent analyses were

TABLE 1

Prevalence of Strabismus Phenotypes Within 615 MZ and 847 DZ Twin Pairs

Phenotype	Number	Prevalence % (95% CI)
Eso-deviation	252	8.6 (7.7–9.7)
Exo-deviation	605	20.7 (19.3–22.2)

TABLE 2

Contingency Tables for MZ and DZ Twin Pairs

Phenotype	Twin 1	Twin 2					
		MZ			DZ		
		Normal	Phoria	Tropia	Normal	Phoria	Tropia
Eso-deviation	Normal	529	13	20	720	27	31
	Phoria	12	9	3	29	5	1
	Tropia	16	3	10	26	1	7
Exo-deviation	Normal	403	55	19	606	77	17
	Phoria	38	60	4	58	54	6
	Tropia	21	4	11	16	5	8

TABLE 3

Model-Fitting Results from Heritability Analyses

Phenotype	Model	$\Delta\chi^2$	Δdf	AIC	<i>p</i>
Eso-deviation	ACE	–3,843.35	...
	AE	0	1	–3,845.35	1.00
	CE	8.21	1	–3,837.13	<.001
	E	63.51	2	–3,783.84	<.001
Exo-deviation	ACE	–2,384.73	...
	AE	21.63	1	–2,365.1	<.001
	CE	0	1	–2,386.73	1.00
	E	154.18	2	–2,234.55	<.001

Note: The model in bold represents the best-fitting model for that phenotype. Abbreviations: A, additive genetic; C, common environment; E, unique environment; $\Delta\chi^2$, chi-square goodness-of-fit statistic; Δdf , change in degrees of freedom between sub-model & full model; *p*, probability that change in χ^2 is zero; AIC, Akaike information criterion.

performed with males and females grouped within zygosity. Table 1 shows the prevalence of strabismus for the two phenotypes examined. For eso-deviation, the polychoric correlation within MZ twin pairs was 0.65 (0.50–0.76) compared with 0.33 (0.14–0.49) for DZ twins, suggesting a genetic role ($p = .003$). Twin pair correlations were similar across zygosity (MZ, 0.55 (0.45–0.64); DZ, 0.53 (0.42–0.62)) for exo-deviation ($p = .86$), implying shared environmental factors are more important for this phenotype. Table 2 displays the summary counts for MZ and DZ twin pairs in a 3×3 contingency table for the ordinal phenotypes examined.

Model fitting analyses of heritability were performed for the two phenotypes investigated, to examine for possible genetic and environmental influences (Table 3). Based on the polychoric correlations an ACE model was initially selected for testing. For eso-deviation, the best-fitting model was AE, with additive genetic effects explaining 64% (50–75%) of the variation in the phenotype and unique environmental effects responsible for the remainder (Table 4). In contrast, variation in exo-deviation could be wholly explained in

TABLE 4

Variance Components Results for Strabismus Phenotypes

Phenotype	A (%) (95% CI)	C (%) (95% CI)	E (%) (95% CI)
Eso-deviation	64 (50–75)	0	36 (25–50)
Exo-deviation	0	54 (46–61)	46 (39–54)

terms of shared (54%) and unique environmental influences. Bivariate analysis of eso-deviation and refractive error revealed a modest phenotypic correlation of 0.20 (0.14–0.26) between the traits. The cross-twin-cross-phenotype correlation for these two traits was 0.17 (0.04–0.31) for MZ twins and 0.12 (0.00–0.25) for DZ twin pairs. Bivariate heritability modeling was subsequently performed, however showed a non-significant additive genetic correlation, $r_g = 0.13$ (–0.13 to 0.45). Additionally, the additive genetic correlation could be constrained to zero without significant loss of model fit, thus indicating that eso-deviation and refraction predominantly do not share common genes. In the bivariate model, the heritability specific to eso-deviation was 59% and that common to both eso-deviation and refraction, 0.9%.

Discussion

Our study has shown that genetic factors are important in the etiology of eso-deviation, while supporting a greater role for environmental factors in the development of exo-deviation. After adjustment for the effects of age, sex, and refractive error, the heritability of comitant eso-deviation was estimated to be 64%. Our study represents the first attempt to quantify genetic and environmental variance in strabismus using a clinical data set based on twin subjects. Familial clustering of comitant strabismus has long been observed and an underlying heritable component for the disorder suspected. However, until recently no attempt has been made to quantify the genetic and environmental components of this relatively common childhood visual dysfunction. The reason for discerning these relative contributions is to improve both our understanding of its etiology and our ability to identify those at risk at an earlier stage. Given the distinctly larger genetic contribution to eso-deviation (as defined in this study), we feel this is an important group to focus limited resources on in future gene-finding efforts.

While there is a relatively large body of twin strabismus literature extending over the past 30 years (Wilmer & Backus, 2009), few studies have attempted to evaluate these data in accordance with modern twin analytical research techniques (Neale & Cardon, 1992). Based on family history and familial concordance, several studies have found that the magnitude of familial contribution to strabismus varies based on the type of deviation, with eso-deviation being most significant (Abrahamsson et al., 1999; Matsuo et al., 2002; Ziakas et al., 2002). Ziakas et al. found that a family

history of strabismus was most frequently reported in cases of hypermetropic accommodative esotropia (26.1% first-degree relatives affected) compared to 4% of first-degree relatives of index cases with exotropia (Ziakas et al., 2002). Greater familial aggregation of esotropia is supported by Podgor et al.'s large cohort study of over 40,000 families, which determined that the odds of esotropia more than doubled for a child if his or her sibling had esotropia (OR 2.6, 95% CI 1.6–4.2), in contrast to a non-significant association observed for exotropia (Podgor et al., 1996). In a recent review and meta-analysis employing SEM techniques to quantify variance components, Wilmer and Backus retrospectively analyzed Podgor's data in conjunction with two other studies (Orlebeke & Koole, 1999; Richter, 1967) selected to satisfy inclusion criteria (Wilmer & Backus, 2009). Genetic modeling revealed a strong effect of genes on the etiology of strabismus, with heritability estimated at 92% for the combined data sets. The primary reason these studies were included in the meta-analysis was that the method of ascertainment was specified. Similarly, we used unselected twin pair volunteers from a population-based sample, thus attempting to minimize potential ascertainment bias that might produce inflated concordance estimates if twin pairs were selected on the basis of one member being affected. Wilmer and Backus also analyzed phoria data from their own unselected sample and found that genetic factors played no role across a mostly sub-clinical range of latent deviations, with a best-fitting CE model ($C = 0.61$, $E = 0.39$).

Phenotypes encompassing heterophorias were included to increase statistical power in our study. The clinical relevance of such a definition may be argued, although our reasoning reflects difficulties encountered in the characterization of endophenotypes for categorical disorders in other fields, psychiatry being a classic example. Bipolar disorder has been shown to be highly heritable mental illness (McGuffin et al., 2003), with linkage studies supporting a complex polygenic basis for the condition (Craddock & Jones, 1999). Additionally, phenotypic heterogeneity associated with diaphanous diagnostic boundaries of the bipolar disorder spectrum has been recognized as a major obstacle in the genetic dissection of the illness (Hasler et al., 2006; MacQueen et al., 2005). Consequently, it has been suggested that genetic and clinical work might consider whether all phenotypic variants of the bipolar spectrum are an expression of a continuous underlying genetic liability (Edvardsen et al., 2008). In a similar way, if strabismus and orthophoria were considered to occupy opposing ends of a clinical spectrum of anomalous ocular deviation, perhaps the same genes influence latent in addition to manifest deviation, and it is thus useful for analysis to group the conditions.

It is likely that we were underpowered to properly assess heritability for strabismus independently in this study. Even though data were available for nearly 1,500 twin pairs, this may be fewer than necessary to reject the CE model when the true model is AE. Neale et al. (1994) constructed

power curves for threshold genetic models in the classic twin study. With a prevalence for esotropia of ~5% in our study and ~1,500 twin pairs, we would have 80% power to detect an additive genetic variance component of ~0.75 (Neale et al., 1994). An alternative way to consider this is that if esotropia were similarly heritable to eso-deviation (i.e., $A = 0.64$), we would require over 2,000 twin pairs (~2,300) to resolve an additive genetic component and reject the CE model (80% power, prevalence ~5%). Other limitations of the present work include its retrospective nature and the potential for recall bias. Additionally, and due to statistical power considerations, stratification of esotropia into subgroups (e.g., infantile, fully/partially accommodative, etc.) while ideal, would lead to such high margins of error as to be uninterpretable. Further large prospective twin studies, with accurate ascertainment of the different subtypes of strabismus, will be important for future genetic linkage or association studies to target those subtypes with the highest genetic risk. Our study nevertheless provides clear guidance on the importance of distinguishing eso-deviations from exo-deviations in genetic studies. Moreover, our study also rejects the possibility that the genetic contribution to strabismus is due primarily to heritable refractive anomalies.

The mode of strabismus inheritance and the identification of associated genetic variants has thus far proven difficult. Genome-wide linkage analysis of comitant strabismus has yielded relatively few chromosomal susceptibility loci. An initial study found loci at chromosomes 7p22.1 (Parikh et al., 2003) and a more recent study (Shaaban et al., 2009), extending previous work by Fujiwara et al. (2003), identified loci at 4q28.3 and 7q3.1. This second study, conducted in 55 Japanese families with at least two cases of comitant strabismus, did not distinguish these cases based on the direction of their deviation. Our findings suggest that future linkage studies could improve statistical power for detecting genetic loci by focusing on esotropia. Additionally, it may be of value to include individuals with esophoria in such work.

The prevalence of manifest strabismus in this study (9.1%) is considerably greater than that reported (2.5–4.0%) in non-twin Caucasian populations (Kvarnstrom et al., 2001; Robaei et al., 2006), but is consistent with that reported in twins (Wilmer & Backus, 2009). A likely explanation for this difference concerns the representativeness of twin data for the general population (Sanfilippo et al., 2011). While the majority of ocular biometric traits have been shown to be similar among twins and singletons, this may not be the case for strabismus. Certainly, it is well accepted that on average, twins are more likely to be born premature and have lower birth weights than singleton pregnancies (Kiely, 1990; Min et al., 2000). Low birth weight has been found to be associated with a three- to four-fold increased risk of strabismus (Bremer et al., 1998; Robaei et al., 2006), potentially accounting for higher prevalence in our study.

In summary, our classic twin study has shown that genetic factors are significant in the etiology of comitant esodeviation, but not of exodeviation, and that the heritability of esodeviation is largely independent of refractive error. These findings provide a more fine-tuned understanding of genetic factors in strabismus. In the clinic, they support an emphasis on genetic risk factors for esodeviations and environmental risk factors for exodeviations. In the lab, they suggest the importance of directed efforts to identify strabismus susceptibility loci specific to esodeviations. Identifying such loci and clarifying their mechanisms of action could improve our understanding of esodeviations and point the way toward novel treatments and preventative measures.

Acknowledgments

This work was financially supported by the Ophthalmic Research Institute of Australia and the Australian National Health and Medical Research Council (NHMRC). PGS is the recipient of an NHMRC postgraduate scholarship. CJH is funded by the UK National Institute for Health Research. DAM is a Pfizer Australia research fellow. CERA receives Operational Infrastructure Support from the Victorian Government.

Disclosure of Interests

No conflicting relationship exists for any author.

References

- Abrahamsson, M., Magnusson, G., & Sjostrand, J. (1999). Inheritance of strabismus and the gain of using heredity to determine populations at risk of developing strabismus. *Acta Ophthalmologica Scandinavica*, 77, 653–657.
- Boker, S., Neale, M., Maes, H., Wilde, M., Spiegel, M., Brick, T., Spies, J., Estabrook, R., Kenny, S., Bates, T., Mehta, P., & Fox, J. (2011). OpenMx: An open source extended structural equation modeling framework. *Psychometrika*, 76, 306–317.
- Bremer, D. L., Palmer, E. A., Fellows, R. R., Baker, J. D., Hardy, R. J., Tung, B., & Rogers, G. L. (1998). Strabismus in premature infants in the first year of life. Cryotherapy for Retinopathy of Prematurity Cooperative Group. *Archives of Ophthalmology*, 116, 329–333.
- Chew, E., Remaley, N. A., Tamboli, A., Zhao, J., Podgor, M. J., & Klebanoff, M. (1994). Risk factors for esotropia and exotropia. *Archives of Ophthalmology*, 112, 1349–1355.
- Christianson, R. E. (1980). The relationship between maternal smoking and the incidence of congenital anomalies. *American Journal of Epidemiology*, 112, 684–695.
- Craddock, N., & Jones, I. (1999). Genetics of bipolar disorder. *Journal of Medical Genetics*, 36, 585–594.
- Cross, H. E. (1975). The heritability of strabismus. *American Orthoptic Journal*, 25, 11–17.
- Edvardsen, J., Torgersen, S., Røysamb, E., Lygren, S., Skre, I., Onstad, S., & Oien, P. A. (2008). Heritability of bipolar spectrum disorders. Unity or heterogeneity? *Journal of Affective Disorders*, 106, 229–240.
- Engle, E. C. (2007). Genetic basis of congenital strabismus. *Archives of Ophthalmology*, 125, 189–195.
- Falconer, D. S., & Mackay, T. F. C. (1996). *Introduction to quantitative genetics*. Harlow, UK: Longman Group.
- Fujiwara, H., Matsuo, T., Sato, M., Yamane, T., Kitada, M., Hasebe, S., & Ohtsuki, H. (2003). Genome-wide search for strabismus susceptibility loci. *Acta Medica Okayama*, 57, 109–116.
- Graham, P. A. (1974). Epidemiology of strabismus. *The British Journal of Ophthalmology*, 58, 224–231.
- Gutowski, N. J., Bosley, T. M., & Engle, E. C. (2003). 110th ENMC International Workshop: The congenital cranial dysinnervation disorders (CCDDs). Naarden, The Netherlands, 25–27 October, 2002. *Neuromuscular Disorders*, 13, 573–578.
- Hakim, R. B., & Tielsch, J. M. (1992). Maternal cigarette smoking during pregnancy. A risk factor for childhood strabismus. *Archives of Ophthalmology*, 110, 1459–1462.
- Hasler, G., Drevets, W. C., Gould, T. D., Gottesman, I. I., & Manji, H. K. (2006). Toward constructing an endophenotype strategy for bipolar disorders. *Biological Psychiatry*, 60, 93–105.
- Jones, W. H. S. (1886). Airs, waters and places. In: F. Adams (Ed.). *The genuine works of Hippocrates* (p.171). New York: William Wood & Co.
- Keith, C. G., & Kitchen, W. H. (1983). Ocular morbidity in infants of very low birth weight. *The British Journal of Ophthalmology*, 67, 302–305.
- Kiely, J. L. (1990). The epidemiology of perinatal mortality in multiple births. *Bulletin of the New York Academy of Medicine*, 66, 618–637.
- Kvarnstrom, G., Jakobsson, P., & Lennerstrand, G. (2001). Visual screening of Swedish children: An ophthalmological evaluation. *Acta Ophthalmologica Scandinavica*, 79, 240–244.
- Mackey, D. A., MacKinnon, J. R., Brown, S. A., Kearns, L. S., Ruddle, J. B., Sanfilippo, P. G., Sun, C., Hammond, C. J., Young, T. L., Martin, N. G., & Hewitt, A. W. (2009). Twins Eye Study in Tasmania (TEST): Rationale and methodology to recruit and examine twins. *Twin Research and Human Genetics*, 12, 441–454.
- MacQueen, G. M., Hajek, T., & Alda, M. (2005). The phenotypes of bipolar disorder: Relevance for genetic investigations. *Molecular Psychiatry*, 10, 811–826.
- Matsuo, T., Hayashi, M., Fujiwara, H., Yamane, T., & Ohtsuki, H. (2002). Concordance of strabismic phenotypes in monozygotic versus multizygotic twins and other multiple births. *Japanese Journal of Ophthalmology*, 46, 59–64.
- McGuffin, P., Rijdsdijk, F., Andrew, M., Sham, P., Katz, R., & Cardno, A. (2003). The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. *Archives of General Psychiatry*, 60, 497–502.
- Min, S. J., Luke, B., Gillespie, B., Min, L., Newman, R. B., Mauldin, J. G., Witter, F. R., Salman, F. A., & O'Sullivan,

- M. J. (2000). Birth weight references for twins. *American Journal of Obstetrics and Gynecology*, 182, 1250–1257.
- Neale, M. C., & Cardon, L. R. (1992). *Methodology for genetic studies of twins and families*. Dordrecht: Kluwer Academic Publishers.
- Neale, M. C., Eaves, L. J., & Kendler, K. S. (1994). The power of the classical twin study to resolve variation in threshold traits. *Behavior Genetics*, 24, 239–258.
- Orlebeke, J. F., & Koole, F. D. (1999). The effects of parental smoking and heredity on the etiology of childhood strabismus: A twin study. *Human Experimental Toxicology*, 18, 304.
- Parikh, V., Shugart, Y. Y., Doheny, K. F., Zhang, J., Li, L., Williams, J., Hayden, D., Craig, B., Capo, H., Chamblee, D., Chen, C., Collins, M., Dankner, S., Fiergang, D., Guyton, D., Hunter, D., Hutcheon, M., Keys, M., Morrison, N., Munoz, M., Parks, M., Plotsky, D., Protzko, E., Repka, M. X., Sarubbi, M., Schnall, B., Siatkowski, R. M., Traboulsi, E., Waeltermann, J., & Nathans, J. (2003). A strabismus susceptibility locus on chromosome 7p. *Proceedings of the National Academy of Sciences USA*, 100, 12283–12288.
- Podgor, M. J., Remaley, N. A., & Chew, E. (1996). Associations between siblings for esotropia and exotropia. *Archives of Ophthalmology*, 114, 739–744.
- Ponsonby, A. L., Brown, S. A., Kearns, L. S., MacKinnon, J. R., Scotter, L. W., Cochrane, J. A., & Mackey, D. A. (2007). The association between maternal smoking in pregnancy, other early life characteristics and childhood vision: The Twins Eye Study in Tasmania. *Ophthalmic Epidemiology*, 14, 351–359.
- R Development Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0. Retrieved April 16, 2010, from <http://www.R-project.org>.
- Richter, S. (1967). Zur hereditat des strabismus concomitans. *Zur Hereditat des Strabismus Concomitans*, 3, 235–243.
- Robaei, D., Rose, K. A., Kifley, A., Cosstick, M., Ip, J. M., & Mitchell, P. (2006). Factors associated with childhood strabismus: Findings from a population-based study. *Ophthalmology*, 113, 1146–1153.
- Sanfilippo, P. G., Hewitt, A. W., Hammond, C. J., & Mackey, D. A. (2010). The heritability of ocular traits. *Survey of Ophthalmology*, 55, 561–583.
- Sanfilippo, P. G., Medland, S. E., Hewitt, A. W., Kearns, L. S., Ruddle, J. B., Sun, C., Hammond, C. J., Young, T. L., Martin, N. G., & Mackey, D. A. (2011). Ophthalmic phenotypes and the representativeness of twin data for the general population. *Investigative Ophthalmology & Visual Science*, 52, 5565–5572.
- Shaaban, S., Matsuo, T., Fujiwara, H., Itoshima, E., Furuse, T., Hasebe, S., Zhang, Q., Qtt, J., & Ohtsuki, H. (2009). Chromosomes 4q28.3 and 7q31.2 as new susceptibility loci for comitant strabismus. *Investigative Ophthalmology & Visual Science*, 50, 654–661.
- Spector, T. D., & Williams, F. M. (2006). The UK Adult Twin Registry (TwinsUK). *Twin Research and Human Genetics*, 9, 899–906.
- Torp-Pedersen, T., Boyd, H. A., Poulsen, G., Haargaard, B., Wohlfahrt, J., Holmes, J. M., & Melbye, M. (2010). Perinatal risk factors for strabismus. *International Journal of Epidemiology*, 39, 1229–1239.
- Traboulsi, E. I. (2007). Congenital cranial dysinnervation disorders and more. *Journal of American Association for Pediatric Ophthalmology and Strabismus*, 11, 215–217.
- Waardenburg, P. J. (1954). Squint and heredity. *Documenta Ophthalmologica Proceedings Series*, 7–8, 422–494.
- Williams, C., Northstone, K., Howard, M., Harvey, I., Harrad, R. A., & Sparrow, J. M. (2008). Prevalence and risk factors for common vision problems in children: Data from the ALSPAC study. *The British Journal of Ophthalmology*, 92, 959–964.
- Wilmer, J. B., & Backus, B. T. (2009). Genetic and environmental contributions to strabismus and phoria: Evidence from twins. *Vision Research*, 49, 2485–2493.
- Wright, M., & Martin, N. (2004). Brisbane adolescent twin study-outline of study methods and research projects. *Australian Journal of Psychology*, 56, 65–78.
- Ziakas, N. G., Woodruff, G., Smith, L. K., & Thompson, J. R. (2002). A study of heredity as a risk factor in strabismus. *Eye*, 16, 519–521.